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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/675,509	FULTON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,10,11,18,19,25-27 and 32* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10,11,18,19,25-27 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 11/7/05, has been entered. Claims 28-31 are cancelled; claims 16, 17 and 20-24 are withdrawn; claims 1, 3, 10, 11, 18, 19, 25-27 have been amended; claim 32 is added; claims 1, 3, 10, 11, 18, 19, 25-27 and 32 are under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 10, 11, 18, 19, 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 15-20 of copending Application No. 10/342,119. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 7/6/05.

Applicants argue that the '119 application provides for the administration for at least one thiamin depleting compound, selected from the group consisting of a thiamin antimetabolite, a thiamin-cleaving compound, and a gene that encodes a

polypeptide that acts as a thiamin-depleting agent. Thus, the requirement for the bacterium of the instant claims is not required for the '119, they do not render the claimed invention obvious.

These arguments are considered, but are not persuasive because the instant application teaches the same methods of inducing apoptosis, and that a thiaminase is considered a thiamin-cleaving agent, further, that both methods are directed to reducing levels of thiamin to induce apoptosis, the claims are obvious over each other. Finally, the '119 claims, wherein specific embodiments are directed to compositions for delivery, and pharmaceutical compositions, the instant claims are encompassed by these embodiments, as the bacterium containing the nucleic acid are considered a composition for delivery or pharmaceutical compositions, because delivery of the bacterium is what is instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 25-27, and newly added 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 7/6/05. This is a new matter rejection, as set forth in the prior Office action.

Applicants argue that the claims, as amended, do not introduce new matter into the disclosure because the specification teaches avirulent and attenuated bacterium, which are considered "non-pathogenic". Thus, Applicants argue that this term is used consistently in the specification to refer to bacteria that have been rendered, or alternatively, are inherently non-pathogenic. Applicants argue that support for the requirement of non-pathogenicity of C. sporogenes and C. beijerinckii, is found in the specification for "avirulent" form of clostridia, which are rendered this way by genetic engineering. Furthermore, Applicants argue that the requirement for non-pathogenicity of Salmonella, and in particular, S. typhimurium, is shown by attenuating the bacterium. Thus, Applicants argue that one of skill in the art would recognize that a bacterium expressing thiaminase could therefore induce apoptosis in vertebrate cells, and that this specification provides adequate support for the claimed embodiment of non-pathogenic bacterium, because the methodology was achieving this was well-known in the art prior to the filing date of the claimed invention. See pages 9-10 of the Response.

These arguments have been fully considered, but are not persuasive. Applicants are arguing limitations that are not in the claims. In particular, that the "preferred embodiments" which genetically modify the bacteria to be non-pathogenic are not found to overcome the breadth of the claims, which introduce new matter to the disclosure. The claims require that the bacterium are non-pathogenic; however, there are no steps with regard to the genetic modification or attenuation of the bacteria in the claims, such that it is readily apparent that this causes the bacteria to be non-pathogenic. Although the specification may provide guidance with regard to transfecting specific prokaryotic cells, there is no specific description with regard to the "non-pathogenic bacteria" as encompassed by the claims. The breadth of these claims encompass bacteria that are non-pathogenic prior to transfection and bacteria that (as asserted by Applicants) are made non-pathogenic by genetic modification or attenuation.

Thus, it is maintained that these amendments introduce new matter into the disclosure, and that the claimed invention as a whole is not adequately described if the claims require essential, or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.,* 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of non-pathogenic bacterium selected from the group consisting of *C. sporogenes, C. beijerinckii, and S. typhimurium*, comprising a recombinant nucleic acid sequence encoding a thiaminase I from N. gruberi, and methods of using such bacterium for inducing apoptosis in vertebrate cells, lacks written description. The specification fails to describe any non-pathogenic bacterium (as encompassed by the claims) that would fall into this genus and could be constructed and used as claimed, and it was unknown, as of Applicants' filing date.

Applicant is reminded that *Vas-Cath Inc. v.* Mahurkar, 19 USPQ2d 1111 [Fed. Cir., 1991] makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Written Description

The prior rejection of claims 1, 3, 11, 25-27 is withdrawn, for written description because the claims now require that the nucleic acid sequence encode thiaminase I from *N. gruberi*.

The prior rejection of claims 18 and 19 is *maintained*, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record advanced in the prior Office action (mailed 7/6/05).

Applicants argue that they have now amended the claims such that they fulfill the written description requirement. With regard to claim 18, application argues that this finds support in the specification for the recitation of 90% over 200 nucleotides, and thus, the claims are fully described. See page 11 of the Response.

This is not persuasive. The specification provides a list of percentages where the nucleotide sequence can be identical to a list detailing numbers of nucleotides. (page 11, lines 21-25). This does not provide support for the claims, which require both 90% identical to an equal length of at least 200 nucleotides. These embodiments are not specifically named together, and thus, the combination of the two lacks a written description. Additionally, the specification does not provide support for a nucleotide sequence is of equal length to 200 nucleotides in length of SEQ ID NO: 3, there is no contemplation of an "equal length" in the specification. Furthermore, the claim recites that the nucleic acid sequence is at least 90% identical to "an equal length sequence of at least 200 nucleotides in length". This lacks written description because, although thiaminase I from *N. gruberi*, as encoded by SEQ ID NO: 3, has been adequately described, as set forth in the prior Office action, there is no specific description provided by the specification for any other sequences with specific percentage identity to specific nucleotides of SEQ ID NO: 3, which, when constructed and used as claimed, would encode thiaminase I from *N. gruberi*, and be capable of inducing apoptosis in vertebrate cells.

Accordingly, the specification fails to meet the written description requirement with regard to the claimed embodiment of nucleic acid sequences encoding thiaminase I isolated from from *Naegleria gruberi*, wherein the nucleic

acid sequence is at least 90% identical to an equal length of at least 200 nucleotides in length of SEQ IDNO: 3 lacks written description.

Enablement

The prior rejection of claims 1, 3, 11, 25-27 and newly added claim 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1. SEQ ID NO: 3, which encodes thiaminase I from *Naegleria gruberi*, vectors containing a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi* operatively linked to a promoter,

2. cells transformed *in vitro* by said vector, and

3. bacterium selected from the group consisting of non-pathogenic, attenuated *C. sporogenes, C. beijerinckii* and *S. typhimurium* comprising a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi.*

The specification does not reasonably provide enablement for the breadth of the claims, which are directed to *in vivo* methods of inducing apoptosis by administration to a selected group of vertebrate cells, a non-pathogenic bacterium selected from the group consisting of *C. sporogenes, C. beijerinckii* and *S. typhimurium* comprising a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi* to said selected group of vertebrate cells, thereby reducing the level of thiamin in said cells sufficiently to induce apoptosis of said cells, methods for delivering a nucleic acid sequence encoding a thiaminase to vertebrate cells *in vivo.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 7/6/05.

The prior rejection is directed to the unpredictibilities associated with *in vivo* gene therapy. Applicants argue that the pending claims neither recite replacement

of a defective gene, nor the transfection of cells with a gene, in order to achieve a desired result of inducing apoptosis in those cells. Thus, Applicants argue that the present invention is not gene therapy, but can be viewed as a method of reducing thiamin by a mechanism external to the cells of the subject vertebrate. Applicants argue that this is analogous to contemplating a pharmaceutical, wherein the non-pathogenic bacterium expressing the thiaminase would fulfill the role of the pharmaceutical, and would sufficiently reduce the level of thiamin in the cell. Applicants argue that the specification provides multiple examples of target cells, and guidance with regard to the targeting of thiaminase (*e.g.*, by localized administration) in order to practice the claimed invention. See page 11-12 of the Response.

These arguments are considered, but are not persuasive. In particular, the claims broadly encompass gene therapy, because they are directed to introducing a bacterium which is transfected with thiaminase I, in order to express that gene of interest to an individual. In fact, the bacterium in the instantly claimed invention can be seen as analogous to *ex vivo* cellular therapy, wherein a cell is transfected with a particular gene of interest, and is administered to a host in order to express a particular gene of interest. The unpredictability in the state of the art of gene therapy has been addressed in prior Office actions. See the Office action, mailed 5/28/02. The invention requires the delivery of thiaminase to appropriate cells in order to induce apoptosis. The bacterium must produce thiaminase in a physiologically relevant level, in an appropriate cell type, in order to induce apoptosis. Although the specification provides prophetic examples of how to target specific cell types, there is no working example with regard to correctly targeting a selected group of cells, using the claimed bacterium, in order to induce apoptosis *in vivo*. The unpredictibilities in the art of gene therapy are not overcome by the teachings of the specification, or any evidence of record. The claims are broadly drawn to inducing apoptosis in any cell type, by any means of administration. The

art previously cited, clearly shows that this is generally unpredictability. As stated previously, target cells would need to be specifically contacted (*i.e.*, is a particular promoter or route of administration critical), and the bacterium must express sufficient amounts of thaiminase in order to induce apoptosis. Furthermore, with regard to the recitation of "non-pathogenic bacterium", it is noted that the specification only provides guidance with regard to genetically engineered *C. sporogenes, C. beijerinckii* and *S. typhimurium* that have been rendered non-pathogenic. The bacterium themselves are pathogenic, and the claims encompass both modified and unmodified bacterium. In order for the bacterium to be non-pathogenic, the claims must reflect this modification.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving thiaminase gene therapy, the lack of guidance or direction provided by the specification to carry out thiaminase gene therapy as broadly claimed, the lack of working examples provided by the specification for the demonstration or correlation to inducing apoptosis or achieving therapeutic thiaminase gene expression *in vivo*, the unpredictable and undeveloped state of the art with respect to the gene therapy art, it would have required undue experimentation for one of skill in the art to make and/or use the claimed vectors, bacterium, and methods of using the same.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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